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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,656	06/22/2006	J. Christopher Anderson	54A-000510US	3238

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QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
GEBREYESUS, KAGNEW H	
ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,656	ANDERSON ET AL.	
	Examiner	Art Unit	
	Kagnew H. Gebreyesus Ph.D	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/17/07 and 8/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response on November 12, 2007 in reply to the Office Action dated August 12, 2007 is acknowledged. Applicants have elected the invention of Group 1 encompassing claims 1-11 and the species of SEQ ID NO: 74 encoding the ORS of SEQ ID NO: 75 with traverse.

Upon further reconsideration of the lack of unity it is acknowledged that the priority for provisional application 60/485451 filed on July 7, 2003 pre-dates the reference used to break unity of invention. The restriction requirement between group 1 and 2 is withdrawn. However the election of species requirement is maintained because each of the ORS molecules comprises a structurally distinct species originating from different organisms. Thus claims 1-23 will be examined with the elected orthogonal tRNA synthetase species of SEQ ID NO: 75 encoded by SEQ ID NO: 74.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141.

Information Disclosure Statement

The information disclosure statement filed on May 17, 2007 and August 27, 2007 for which a copy of the patent publication has been submitted in this application has been considered as shown by the Examiners signature next to each reference.

Oath/Declaration

The oath or declaration submitted on June 22, 2006 has been reviewed and is in compliance with 37 CFR 1.56.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The claimed glutamyl-tRNA composition in 1-23 are claimed in terms of suppressor efficiency of a selector codon as compared to the suppressor efficiency of the specific tRNA of SEQ ID NO: 67 which is an artificial tRNA derived from a consensus of archaeal tRNAs further comprising a G:C at position 10:28. Applicant's specification teaches that suppression efficiency is measured by ampicillin IC_{50} values in *E. coli* comprising both Glu-tRNA synthetase and a Glu-tRNA. However the claims do not recite the structure of any cognate tRNA synthetase from any source in the composition or in the cell. Furthermore the specification teaches that suppressor efficiency varies depending on the cognate synthetase used. Foe example, paragraph [207] of the specification teaches; "cells co-expressing SEQ ID NO: 67 with PhERS display ampicillin IC_{50} values of 212 µg/mL while cells co-expressing SEQ ID NO: 67 with and MmERS display ampicillin IC_{50} values of 450 µg/mL. Thus the metes and

bounds of the relative efficiency (50% suppression efficiency) as claimed in claims 1-23 is indefinite.

Claims 1-23 are further rejected for the recitation "at least about 50%". The term "at least about" is confusing as "at least" and "about" are contradictory terms. "About is a term that expresses 'more or less than', thus as used with the term "at least" the claim is rendered indefinite. Clarification is required.

Furthermore a suppressor efficiency of SEQ ID NO: 67 or the claimed genus of tRNAs with about 50% suppressor efficiency will vary depending on the cognate synthetase used. However the claims do not recite what specific cognate synthetase is used with the tRNA of SEQ ID NO: 67. The identity of the tRNA synthetase used is essential in comparing the recited "about 50% suppressor efficiency" . For examination purposes the cognate synthetases used with the tRNA of SEQ ID NO: 67 are the same as the one in the claimed composition or co-expressed in the cell.

Claim 4 is rejected because the claim recites "...wherein the glutamy-tRNA comprises or is encoded by a polynucleotide sequence as set forth in SEQ ID NO: 67(AE(GC)tRNA), **or** a complementary polynucleotide sequence thereof". However the complementary sequence does not encode the tRNA. Applicants may amend the claim by replacing "or" with "and".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-16, 18-23 are drawn to a composition comprising any orthogonal glutamyl-tRNA (Glu-O-tRNA) from any source including any bacteria, yeast, algae, human etc, wherein said Glu-O-tRNA comprises at least a 50% suppression efficiency in the presence of any cognate synthetase from any source or in the presence of any of the cognate synthetase of SEQ ID NO: 69, 73, 75 or 77 (claim 7, 8) in response to a selector codon as compared to the glutamyl-tRNA corresponding to a polynucleotide as set forth in SEQ ID NO: 67 (AE(GC)tRNA) and any cognate synthetase or the cognate synthetases of SEQ ID NO: 69, 73, 75 or 77 (claims 7 and 8) or conservative variants (claim 17).

As discussed above, suppressor efficiency of a composition depends on the structure of both the glutamyl-tRNA (Glu-O-tRNA) and the glutamyl-tRNA synthetase (Glu-tRS). The specification teaches that the consensus sequence of SEQ ID NO: 67 derived from a cluster of glutamyl-tRNA sequences derived from a number of

archaebacteria suppress a selector codon with a range of efficiencies when used with cognate tRNA synthetase from *Archaeoglobus fulgidus* (AfRS) (SEQ ID NO: 69), *Methanosarcina mazei* (MmRS) (SEQ ID NO: 73), *Methanobacterium thermoautotrophicum* (MtRS) (SEQ ID NO: 75), or *Pyrococcus horikoshii* (PhRS) (SEQ ID NO: 77) in a composition or co-expressed in a cell.

However Applicants are not in possession of all possible glutamyl-tRNAs from any source with any structure and any complementary cognate synthetase from said any source that display 50% suppressor efficiency to the tRNA of SEQ ID NO: 67 wherein the efficiency of SEQ ID NO: 67 is measured in the presence of said any cognate synthetases from any source. The suppressor efficiency for the tRNA of SEQ ID NO: 67 and any cognate synthetase must first be determined before one of skill in the art can determine 50% suppressor efficiency for any tRNA. However the specification only shows the suppressor efficiency for the tRNA of SEQ ID NO: 67 when used in conjunction with a few glutamyl-tRNA synthetases of SEQ ID NO: 69, 73, 75 or 77. The claims however encompass a genus of cognate tRNAs described only in terms of function (i.e. about 50% efficiency). However said 50% efficiency for any **tRNA/synthetase pair from any source must be empirically determined and then compared to the suppressor efficiency of the tRNA of SEQ ID NO: 67 and said any tRNA synthetase.**

The disclosure of the structure of the Glu-tRNA of SEQ ID NO: 67 and a few cognate synthetases from archaebacteria are not sufficient to provide description for the

genus of Glu-tRNA molecules claimed. The specification does not provide a correlation between the structure of any glutamyl-tRNA and glutamyl-tRNA synthetase and the level of suppressor efficiency achieved when used in a composition or when co-expressed in a cell.

Thus the specification does not convey to the skilled artisan that Applicants were in possession of all Glu-O-tRNA molecules from any source with any structure wherein said tRNA molecules exhibit a suppressor efficiency of at least 50% in the presence of any cognate Glu-RS from any source or with the tRNA synthetase of SEQ ID NO: 75 (MtRS) or conservative variants thereof (claim 17).

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as structure, formula [or] chemical name, 'of the claimed subject matter sufficient to distinguish it from other material. " For claims drawn to a genus, MPEP § 2163 states the written description required for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by a disclosure of relevant identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus.

Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The specification teaches that suppressor efficiencies of Glu-O-tRNA of SEQ ID NO: 67 depend on the structure of Glu-RS used. For example the PhRS of SEQ ID NO: 77 displays a suppressor efficiency of 212 µg/mL when used with the Glu-tRNA of SEQ ID NO: 67. The MmRS of SEQ ID NO: 73 displays a suppressor efficiency of 450 µg/mL when used with the same Glut-RNA of SEQ ID NO: 67. Furthermore even if the structure of the cognate Glu-RS in the composition were described (such as SEQ ID NO: 69, 73, 75, 77), the claims still encompass a genus of Glu-O-tRNA molecules described by function (suppressor efficiency) because, the specification does not teach an identifying characteristic for any tRNA that can ensure the claimed "about 50% suppressor efficiency" on a selector codon.

Thus a genus of Glu-tRNA and/or Glu-RS that fit a desired functional limitation is claimed. However applicants are not in possession of the claimed genus of Glu-tRNA and/or cognate Glu-RS pair.

The disclosure of a single Glu-tRNA of SEQ ID NO: 67 and the few disclosed species of Glu-RS are not representative for the genus of tRNAs with at least 50% suppressor efficiency because, to fully describe a genus of Glu-tRNA, Applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics when coupled with a known or disclosed correlation between function and structure, or a combination thereof.

However as stated above since suppressor efficiency of any Glu-tRNA/Glu-RS must be determined empirically, one skilled in the art cannot predict the structure of the claimed genus of Glu-tRNA molecules that suppress a selector codon with at least 50% efficiency.

Given this lack of description of representative species encompassed by the genus of the claim, the specification does not sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because while the specification is enabling for a composition or a cell co-expressing SEQ ID NO: 67, a consensus designed tRNA with a G:C pair at position 10:28 (AE(GC)) with the tRNA synthetase of AfERS (SEQ ID NO: 68), MmERS (SEQ ID NO: 72), MtERS (SEQ ID NO: 74), or PhERS (SEQ ID NO: 76) that display IC_{50} suppressor efficiency that is 4-5-fold greater than those of cells co-expressing the a less active tRNA also a consensus designed tRNA with a G:U at position 10:28 (AE(GU)) does not provide enablement for a composition or cell comprising any Glu-O-tRNA/cognate glutamyl-tRNA synthetases

pair wherein said pair show at least 50% suppression efficiency when compared to the suppressor efficiency of SEQ ID NO: 67 (AE(GC) tRNA) and any cognate synthetase (claims 1-23) or any tRNA synthetase including but not limited to the synthetases of SEQ ID NO: 69, 73, 75, 77.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988). The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

In the instant case, the amount of direction and guidance provided is insufficient because the suppressor efficiency of a selector codon varies depending on the structure of both the tRNA and the tRNA synthetase used. Applicants teach glutamyl-tRNA synthetases from *Archaeoglobus fulgidus (AfRS),* a *Methanosarcina mazei (MmRS),* a *Methanobacterium thermoautotrophicum (MtRS),* and *Pyrococcus horikoshii (PhRS)* which were used with the glutamyl tRNA derived from a consensus of archaeal tRNA molecules which further comprise a G:C base pair at position 10:28 (SEQ ID NO: 67) to

suppress a selector codon. The specification teaches that suppressor efficiency was assessed using an ampicillin IC_{50} assay in cells co-expressing SEQ ID NO: 67 (comprising a G:C at position 10:28) and synthetases from *Archaeoglobus fulgidus (AfRS),* a *Methanosarcina mazei (MmRS),* a *Methanobacterium thermoautotrophicum (MtRS),* and *Pyrococcus horikoshii (PhRS).* Cells co-expressing the MmERS/SEQ ID NO: 67 pair exhibited a suppressor efficiency of IC_{50} value of 450 µg/mL, while cells co-expressing the PhERS/SEQ ID NO: 67 pair exhibited an IC_{50} value of 212 µg/mL compared to cells co-expressing said tRNA synthetases and a tRNA comprising a GU at position 10:28. However the breadth of the claims encompasses any composition or cell co-expressing any glutamyl-O-tRNA with any structure and any tRNA synthetase from any source wherein said tRNA suppresses a selector codon with an efficiency of at least 50% compared to the efficiency of SEQ ID NO: 67. in the presence of said *any cognate synthetase from any source*.

However, the nature of the invention is such that the efficiencies of the claimed orthogonal tRNA synthetase must be determined empirically. The specification teaches how to determine suppressor efficiencies for a few glutamyl-tRNA synthetases/tRNA pairs using ampicillin IC_{50} values. Cells comprising the best suppressors can survive in a media with the highest ampicillin concentration. Thus a composition comprising any glutamyl-O-tRNA that suppresses a selector codon with at least 50% efficiency compared to the efficiency of the tRNA of SEQ ID NO: 67 in the presence of a cognate synthetase must also be determined empirically for each glutamyl-tRNA/synthetase

pair. Furthermore the point of reference must also comprise both tRNA/synthetase in order to make a fair comparison. However the specification does not provide any direction or guidance for the suppressor efficiency of the tRNA of SEQ ID NO: 67 because the efficiency is determined with any cognate tRNA synthetase as encompassed in the claims. Thus determining a composition comprising at least 50% suppressor efficiency will vary depending on the cognate tRNA synthetase used.

Therefore the claims encompass an enormous scope wherein a 50% suppressor efficiency for any Glu-tRNA/Glu-RS pair must be empirically be determined relative to suppressor efficiency of SEQ ID NO: 67 and any cognate tRNA synthetase from any source with any structure. Even if the Glu-tRS in the composition was defined with structure (e.g. SEQ ID NO: 69, 73, 75, 77 encompassed in claims 7 and 8, the claims still encompass an enormous scope because the claims are not limited to tRNA from any source with any structure. The structure of the tRNA with 50% efficiency must be empirically determined. Thus the specification does not teach how to make and/or use the invention commensurate in scope with the claims.

Furthermore the standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experiments required to identify all possible Glu-tRNA that suppress a selector codon with 50% efficiency compared to the Glu-tRNA of SEQ ID NO: 67 and any cognate Glu-tRNA synthetase (including but not limited to the synthetases of SEQ

ID NO: 69, 73, 75 and 77) and structurally unknown tRNA and tRNA synthetases is enormous.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific cognate Glu-tRNA /synthetase pairs or what specific structures must be conserved to enable at least a 50% efficiency when compared to the tRNA of SEQ ID NO: 67 and a synthetase assumed to have 100% efficiency. Without such a guidance, the experimentation left to those skilled in the art is undue.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H. Gebreyesus PhD whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nashed/
Nashaat T. Nashed, Ph. D.
Primary Examiner, Art Unit 1656

Kagnew H Gebreyesus
Examiner, Art Unit 1656